POSTGRADUATE RESEARCH CONFERENCE 2015

22 MAY 2015, 9:15 - 16:00. Allam Lecture Theatre & Derwent Cafe, University of Hull
Hull York Medical School (HYMS) and the University of Hull are delighted to welcome you to the Fourth Annual HYMS Postgraduate Conference.

HYMS postgraduate research conference was conceived as a platform to strengthen the social and professional matrix of the medical school through the dynamic exchange of ideas between the research colleagues. The past HYMS postgraduate conferences have been proclaimed a success, and we hope to continue the tradition.

HYMS thrives on the ideals of innovation and creativity. As an extension of the same, this year we are introducing 3-minute thesis presentations alongside the traditional oral and poster presentations. HYMS research conference 2015 shall host nine oral presentations, 24 poster presentations and ten 3-minute thesis presentations.

We thank everyone who submitted the participants, the panel for providing valuable feedback, the organising committee and the attendees for making this possible. We would also like to extend our sincere gratitude to Professor Deborah Smith, Pro-Vice Chancellor for Research from the University of York for agreeing to be a part of our endeavour.

We hope you enjoy the conference and I look forward to meeting you! You can find me at the buffet!

All the Best
Arti and Yama
Programme

09:15 - 10:00  Registration; tea and coffee in Derwent Cafe

10:00 - 10:10  Welcome and introduction

10:10 - 11:10  Presentation Session 1

10:10 - 10:25  Jamilla Hussain, 'The extent, mechanism and method of analysing missing data in palliative care randomised controlled trials: a systematic review'

10:25 - 10:40  Ann Hutchinson, 'Breathing Space: A systematic literature review and qualitative synthesis'

10:40 - 10:55  Simon Fraser, 'Peripheral Blood Leukocyte Immune Responses are Distinctly Altered in Sarcoidosis'

10:55 - 11:10  Four 3 minute thesis presentations

  Thomas Cunningham, 'The relationship between Vitamin D levels in PCOS and non-PCOS patients undergoing subfertility treatment'

  Ehtesham, 'Intra-Individual correlation between Flow mediated dilation (FMD) and Reactive hyperaemia peripheral arterial tonometry RH-PAT in PCOS and Control'

  Jonathan Knaggs, 'The effect of fenamic acid derivatives on TRPA1'

  Flavia Swan, 'Airflow for the relief of chronic refractory breathlessness in patients with advanced cardio-respiratory diseases and mild hypoxaemia or normoxaemia'

11:10 - 11:30  Coffee break in Derwent Cafe

11:30 - 12:30  Presentation Session 2

11:30 - 11:45  Alison Bravington, 'Setting survivorship in context: Exploring experiences of recovery among cancer patients treated with intent to cure'

11:45 - 12:00  Lee Partington, 'Electroimmunoassay Platforms for Point of Care Pregnancy Detection'

12:00 - 12:15  Kayleigh Brocklesby, 'Development of a PET radioligand for imaging angiogenesis for oncology applications'
12:15 - 12:30 Three 3 minute thesis presentations

Ramsah Cheah, 'Exploiting the microfluidic culture to determine the radio-sensitivity of head and neck squamous cell carcinoma tissue'

Lily Oguh, 'The invitro effect of novel receptor tyrosine kinase inhibitors on mesothelioma cells'

Nina Purvis, 'Optimisation of Intravoxel Incoherent Motion (IVIM) Imaging for Breast Cancer with Clinical Results'

12:30 - 13:45 Buffet lunch, served in Derwent Cafe and poster presentation session
Delegates are invited to this dedicated poster presentation session and join more than 20 students who will be presenting their posters

14:00 - 15:00 Presentation Session 3

14:00 - 14:15 Casey Woodward, 'The role of phospholipase Cγ2 in hyperlipidaemia induced platelet activation'

14:15 - 14:30 Robert Law, 'Protein kinase A regulates platelet phosphodiesterase 3A through an A-kinase anchoring protein dependent manner'

14:30 - 14:45 Gill Buchanan, 'Outcomes of Transcatheter Aortic Valve Implantation According to Sex: A Multi-Centre Collaborative Study'

14:45 - 15:00 Three 3 minute thesis presentations

Andrew Ladwiniec, 'Angioplasty of Chronic Total Coronary Occlusions: is there a long-term prognostic benefit? A Propensity Matched Retrospective Cohort Study'

Claire Reid, 'What is Important to Patients Requiring Haemodialysis Treatment? A Thematic Synthesis of Qualitative Studies'

Arti Trivedi, 'Association of Type 1 Inositol 1,4,5-Trisphosphate Receptor (IP3R1) with Protein Kinase A and A-Kinase Anchoring Protein 9 (AKAP9) in platelets'

15:00 - 15:15 Coffee break in Derwent Cafe

15:15 - 15:50 Keynote speaker
Professor Deborah Smith, Pro-Vice Chancellor for Research, University of York
'A career in the biosciences - passion, parasites and people'

15:50 - 16:00 Prize giving and closing remarks by Professor Trevor Sheldon, Dean of HYMS
Prizes will be awarded to the best oral, poster and 3 minute thesis presentations

16:00 Conference closes

During the conference, a photographer will be taking some publicity photographs. The photos, which may be stored electronically by HYMS, will only be used in connection with the activities of HYMS or its parent Universities, and will not be made available for use by any third party. If you have any concerns about this, please contact the HYMS Communications Office (communications@hyms.ac.uk).
10:10 - 10:25 Jamilla Hussain
The extent, mechanism and method of analysing missing data in palliative care randomised controlled trials: a systematic review

Hussain, J.A., Bland, M., Langan, D., White, I., Currow, D., Johnson, M.

Background: In palliative care trials involving patients with advanced, life-limiting illnesses, missing data (MD) are recognised to pose a significant risk of bias and to reduce study power. The extent, mechanisms and methods of handling MD currently employed in this area are unknown.

Method: CENTRAL, OVID Medline and EMBASE were searched from April 2009-2014, with no language restriction. Studies included were randomised controlled trials involving adult patients with advanced, life-limiting illnesses, testing a palliative intervention. Two reviewers independently screened, selected and extracted data (kappa 0.62-1.00).

Results: Of 1,923 papers screened, 108 trials involving 15,560 participants were included: average age 65 years, 74% diagnosed with cancer, median survival 118 days. The trials were conducted over five continents: 40.7% multicentre trials; 32.4% phase 2, pilot or feasibility trials.

The median proportion of incomplete outcome data for the primary endpoint was 20.8% (interquartile range: 5-37.3%). The proportion of MD increased as follow-up time increased. 26.5% of MD was reported as due to death and 14.7% due to illness. 21.2% were reported as ‘withdrawal’ or ‘lost to follow-up’ only. 19% were due to other reasons: 31% of these related to patient/carer factors and 64% to trial design/conduct features. The most frequent method of handling MD, regardless of the extent or mechanism, was complete case analysis (59%). Only 15 studies reported a sensitivity analysis.

Conclusion: The extent of MD was greater in studies involving patients with advanced, life-limiting disease, than that reported in general medical journals as a whole (6-10%). Thus MD poses a greater risk of bias and type two error in such trials. Despite this, the data that were provided were often handled using ad-hoc methods; this has potentially significant clinical, ethical and cost-effectiveness implications.

10:25 - 10:40 Ann Hutchinson
Breathing Space: A systematic literature review and qualitative synthesis

Background: Chronic breathlessness is a common symptom of cardiorespiratory conditions, which has wide-reaching effects on the lives of patients and their families.

This qualitative literature review explores the experience of people living with daily breathlessness due to chronic medical conditions with regard to their beliefs about, coping with and help-seeking for their breathlessness.

Methods: A systematic search of qualitative studies was conducted. The search strategy was guided by search terms for breathlessness (exposure); patient, carer and healthcare professionals (population); and experience, interaction, help-seeking, coping and beliefs (outcomes) combined with a validated qualitative research filter.

The following electronic databases were searched: Medline, PsycINFO, Embase CINAHL (Jan 1987 – July 2014). Titles, abstracts and retrieved papers were independently reviewed by two reviewers and disagreements resolved by a third. Inclusion criteria: English; reported the experience of breathlessness; presented primary empirical qualitative data.

Data (direct quotations from participants) were extracted and managed using NVivo. A thematic synthesis of the selected qualitative studies was conducted.

Results: Seventy seven studies were included. Three major themes were identified: biopsychosocial effects of breathlessness, engaged/disengaged coping, clinician response to patients' breathlessness. The concept of “breathing space” was derived from these themes to represent the findings.

Conclusions: Breathlessness has widespread and often devastating effects on the patient and their families. The coping strategies adopted by the patient and their healthcare professionals’ response to the patients’ breathlessness and clinicians engage with breathlessness using pro-active management in order to maintain reasonable quality of life whilst living with a chronic condition causing breathlessness.
Peripheral Blood Leukocyte Immune Responses are Distinctly Altered in Sarcoidosis

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Sarcoidosis is a multi-system granulomatous inflammatory disease characterised by increased tissue levels of Th1-like cytokines such as IFN-γ and TNF-α. Diminished immune responses have been reported in peripheral blood, yet the reasons for the difference between local and peripheral immunity are not understood. The aim of this study was to investigate whole blood cytokine release in sarcoidosis in response to polyclonal immune activators. The cohorts comprised healthy volunteers (n=22) and subjects diagnosed with sarcoidosis after multidisciplinary assessment (n=18). A whole blood assay system was used to assess cytokine profiles in response to mitogenic and non-mitogenic activators by ELISA. The constituents of the leukocyte populations were analysed by flow cytometry.

In sarcoidosis, the total number of peripheral blood mononuclear cells was lower than in healthy volunteers (1.3x10^6 ±0.09 vs 2.4x10^6 ±0.18 cells/ml, p<0.001), principally due to reduced T-lymphocyte subsets. Stimulation of whole blood with phytohaemagglutinin (PHA) or wheat germ agglutinin (WGA) lead to concentration-dependent increases in IFN-γ and TNF-α release that were significantly greater in sarcoidosis compared with controls (WGA 100µg/ml: TNF-α = 2.8 ±1.0 vs 1.4 ±0.4 ng/ml, p<0.05). Inflammatory cytokine release in response to Staphylococcus enterotoxin A (SEA) was diminished in sarcoidosis consistent with the reduced number of T-lymphocytes. IL-6 release was increased more than two fold in sarcoidosis at 100µg/ml of PHA (195 ±37.5 vs 95 ±16.9 ng/ml, p<0.001), but reduced in response to WGA and SEA when compared with healthy donors. IL-10 release from sarcoidosis blood was not reduced when compared with healthy subjects.

Our findings suggest that peripheral blood leukocytes in sarcoidosis retain the capacity for a resolute inflammatory cytokine responses to certain polyclonal immune activators in spite of a deficiency in the number of peripheral T-lymphocyte cells.

Setting survivorship in context: Exploring experiences of recovery among cancer patients treated with intent to cure

Aims: This project aims to explore cancer survivorship as it is lived out, day-to-day, and investigate how social interaction, social networks and resources in the home and local environment shape the experience of recovery.

Methods: Thirty breast, colorectal and prostate cancer patients treated with intent to cure are being purposively sampled within twelve months of first-line treatment. Each participant takes part in two in-depth interviews, six months apart. Participant photography is used as a basis for dialogue. Following the principles of constructivist grounded theory, data analysis has been ongoing during fieldwork.

Results: Themes emerging from first interviews demonstrate how the resources available within the family, the workplace and the public domain shape the way that meanings are made about cancer diagnosis and treatment, and how these meanings translate into psychological strategies for coping with cancer.

Conclusion: Supportive care after cancer requires an approach which is firmly embedded in social context. From the patient perspective, social resources frame the meanings made from cancer, and inform strategies for coping.
11:45 - 12:00 Lee Partington

**Electroimmunoassay Platforms for Point of Care Pregnancy Detection**

Lee I. Partington, Jay Wadhawan

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The early determination of pregnancy and approximate gestational age is extremely important for female patients in various clinical settings such as Accident and Emergency and wards. The accurate exclusion of pregnancy is compulsory preceding medical interventions and preventative care, for instance surgery, chemotherapy and abdominal X-ray in order to minimize or avoid health risks to the unborn child and/or patient. The current healthcare system is deficient of reliable, portable and quantitatively validated point of care (POC) routes for the rapid diagnosis of pregnancy in urine, relying on qualitative, poor accuracy ‘wand’ testing or complicated, labour intensive and lengthy (4-6 hour) lab based assay methods unsuitable for point of care testing methodologies, where rapid quantitative data is commonly required.

The development of a molecular wire based electroimmunoassay platform for the rapid (ca. 20 mins) quantitative detection of human chorionic gonadotropin (hCG) for the POC is reported. An electrode surface was modified to provide a multilayered interface to which ferrocene labelled anti-hCG antibodies were covalently bound. The physicochemical dynamics of this biosensor are examined and exploited to afford rapid (20 min) detection of the analyte in artificial urine with linear calibration within the range 1 pg mL-1 to 1 μg mL-1 (9.3x10^{-3} mIU mL-1 – 9.3x10^3 mIU mL-1), viz. covering the full clinical range whilst retaining the accuracy and sensitivity required. The limit of detection at 1.93 mIU mL-1 and no evident “high dose hook effect”, verify the clinical utility of the sensor.

12:00 - 12:15 Kayleigh Brocklesby

**Development of a PET radioligand for imaging angiogenesis for oncology applications**

Introduction: Angiogenesis is a survival mechanism utilised by tumours in response to a critical deficiency in nutrient supply. The importance of this process is recognised by its position as a hallmark of cancer. There exists an urgent requirement for accurate evaluation of drug receptor expression across the whole tumour and between lesions in metastatic disease to successfully deliver on the goal of personalised therapy. Positron emission tomography (PET) is a minimally invasive technique ideally suited to translational imaging of angiogenesis.

Vascular endothelial growth factor receptor 2 (VEGFR2) is an attractive target due to its importance as a key mediator of angiogenesis. Overexpression of VEGFR2 and its ligand, VEGFA, correlates with poor prognosis. Currently there are no imaging probes available which target the intracellular nucleoside binding pocket. Therefore this project is focussed on the development of a novel radioligand which binds to the nucleoside binding pocket of VEGFR2.

**Methods**

**Chemistry:** Two libraries of compounds were designed based on the following principles: cLogP values (<4), retention of VEGFR2 affinity, selectivity and an easily incorporated motif for radiolabelling.

**Biology:** Initial screening comprised of cell viability assays (MTS) to select lead candidate(s) by their effects on proliferation. The lead candidates were subjected to further in vitro immunofluorescence assays to look for apoptosis with DAPI staining.

**Results**

**Chemistry:** Two libraries compounds were synthesised and fully characterised.

**Biology:** Cellular proliferation was assessed in low expressing (HCT116) and high expressing (A549) cell lines, 9 (library A) exhibited the greatest effect on cellular proliferation. Immunofluorescence studies highlighted nuclei with fragmented DNA in both the HCT116 and A549 cell lines, which cannot be attributed to apoptosis.

**Conclusions**

Two libraries of compounds (with different core scaffolds) were synthesised and fully characterised. Library A were interrogated for potential off-target effects, through the use of cellular viability and immunofluorescence assays. Initial screening of library A concludes their unsuitability for PET imaging. Library B is currently being assessed for their suitability for PET imaging.
The role of phospholipase C \( \gamma_2 \) in hyperlipidaemia induced platelet activation

Introduction: Oxidised low-density lipoproteins (oxLDL) are a highly atherogenic particle that circulates in the blood of individuals with cardiovascular diseases. Furthermore, oxLDL has been proposed as a potential mediator of platelet hyperactivity & prothrombotic phenotype. Previously we have shown that oxLDL activates platelets through the receptor CD36. However, the molecular mechanisms underpinning this activation are unclear. One key protein believed to be involved is phospholipase C gamma 2 (PLC\( \gamma_2 \)), an enzyme responsible for PKC activation and calcium mobilisation. PLC\( \gamma_2 \) is known to be critical to platelet activation in response to the traditional platelet agonists collagen, fibrinogen and von Willebrand factor. However its role in signal transduction downstream of oxLDL is unknown.

Aim: To determine the role of PLC\( \gamma_2 \) in the activation of platelets in response to oxLDL.

Methods: In order to investigate PLC\( \gamma_2 \) phosphorylation, immunoprecipitation and immunoblotting techniques were used. PLC\( \gamma_2 \) activity was measured using mass spectroscopy. To test platelet adhesion and spreading function, platelets were stained and incubated with either immobilised oxLDL or flowed through coated capillary tubes.

Results: OxLDL induced tyrosine phosphorylation on numerous proteins in platelets, including PLC\( \gamma_2 \). OxLDL induced concentration and time-dependent phosphorylation of PLC\( \gamma_2 \) on the two known activatory sites - Tyr753 and Tyr759. These phosphorylation events were associated with activation of the enzyme. The CD36 neutralising antibody FA6.152 blocked oxLDL induced phosphorylation of PLC\( \gamma_2 \). Pharmacological inhibition of the tyrosine kinases Src and Syk, but not PI3-kinase, also blocked PLC\( \gamma_2 \) phosphorylation. Chemical inhibition or genetic ablation of PLC\( \gamma_2 \) or CD36 prevented platelet spreading on oxLDL. These data indicate that PLC\( \gamma_2 \) is activated in a CD36 manner and requires both Src and Syk kinases.

Conclusions: We show that oxLDL is able to activate PLC\( \gamma_2 \) via a CD36 – SFK – Syk pathway resulting in the activation of platelets.

This work is funded by Heart Research UK (CJW) and the British Heart Foundation (KSW).

Protein kinase A regulates platelet phosphodiesterase 3A through an A-kinase anchoring protein dependent manner

Objectives: Controlling inappropriate blood platelet activity is critical to protecting against arterial thrombosis. Endogenous platelet inhibitory mechanisms are mediated by prostacyclin (PGI2) stimulated cAMP signalling, which is propagated and terminated by protein kinase A (PKA) and phosphodiesterase 3A (PDE3A), respectively. However, the tight spatiotemporal regulation of this signalling pathway that allows it to facilitate haemostasis while inhibiting thrombosis is unclear. In this study we examined the control of cAMP signalling and discovered a novel A-kinase anchoring protein (AKAP) signalling complex that integrates propagation and termination of cAMP signalling through coupling of PKA and PDE3A.

Methods: Signalling events and protein complexes were investigated using immunoprecipitation techniques on washed platelets. PDE3A activity was assessed using a colorimetric assay and platelet cAMP concentrations were measured using ELISA.

Results: PGI2 induced a dose and time-dependent increase phosphorylation of PDE3A at serine312 in a PKA-dependent manner. This phosphorylation event was associated with an increase in phosphodiesterase enzymatic activity. The phosphorylation and activation of PDE3A was blunted by a cell permeable inhibitor of PKA-AKAP interactions, suggesting that cAMP-signalling induced enzyme activation occurs through an AKAP-mediated mechanism. Using a cAMP-pull down approach combined with immunoblotting, we confirmed the presence of multiple isoforms of AKAP7 (\( \delta \) and \( \gamma \)). To examine the possibility of a multi enzyme complex we used a co-immunoprecipitation approach. Immunoprecipitation of PDE3A led to the co-association of both type II PKA and AKAP7-\( \delta \). Importantly, when reverse immunoprecipitation of AKAP7 was performed we found the association of PD3A and type II PKA, and associated PDE and PKA activity.

Conclusion: This is the first evidence for spatiotemporal regulation of cAMP signalling in blood platelets and suggests the presence of a PDE3A/PKA/AKAP7 signalling complex that regulates PGI2 mediated platelet inhibition.

This work was funded by the BBSRC and University of Hull.
Outcomes of Transcatheter Aortic Valve Implantation According to Sex: A Multi-Centre Collaborative Study

Background: Women present with aortic stenosis at a later age than men and have more co-morbidities. There is minimal data available evaluating the outcomes of transcatheter aortic valve implantation according to sex.

Methods: The databases of 4 experienced European centers were pooled and analyzed. Due to differences in baseline clinical characteristics, propensity score matching was performed. Study objectives were VARC outcomes at 30-days and mid-term follow-up.

Results: In total, 1,125 patients were included: 532 (47.3%) women and 593 (52.7%) men. After propensity matching, 344 patients were identified in each group. At 30-days, there were no differences in all-cause mortality (women 5.6% vs. men 6.2%; OR 1.116; 95% CI 0.589-2.115; p=0.737), cardiovascular mortality (4.1% vs. 4.7%; OR 1.153; 95% CI 0.554-2.402; p=0.703), peri-procedural myocardial infarction (1.2% vs. 0.6%; OR 0.497; 95% CI 0.090-2.732; p=0.421), stroke (1.7% vs. 1.7%; OR 1.000; 95% CI 0.319-3.132; p=1.000), stage 3 acute kidney injury (5.2% vs. 5.8%; OR 1.125; 95% CI 0.584-2.166; p=0.725) or device success (93.6% vs. 95.3%; OR 1.405; 95% CI 0.725-2.724; p=0.314). Conversely, women had more major vascular complications (14.6% vs. 6.7%; OR 0.420; 95% CI 0.250-0.705; p=0.001) and life-threatening bleeding (18.7% vs. 9.3%; OR 0.447; 95% CI 0.284-0.704; p=0.001), corresponding to a difference in the combined safety endpoint (29.9% vs. 22.6%; OR 0.685; 95% CI 0.486-0.965; p=0.031) favouring men. At a mean follow-up of 503 days, although no difference in cardiovascular mortality (13.2% vs. 16.0%; OR 1.246; 95% CI 0.880-1.750; p=0.204), women had a lower all-cause mortality (22.6% vs. 30.2%; OR 1.480; 95% CI 1.131-1.936; p=0.004).

Conclusions: Women undergoing transcatheter aortic valve implantation had superior survival compared to men at mid-term follow-up, despite more vascular complications and life threatening bleeding initially. More work is needed in this field to ascertain the best treatment strategy for patients with aortic stenosis requiring intervention.
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Miriayi Aibibula
Metabolic Regulation of Platelets

Mufuliat Adesanya
Procoagulant Activity of Tumour Microparticles on Endothelium

Christopher Dalgliesh
The relationships between socioeconomic status and place on death

Michael Fox
Minkowski Functionals in MRI: A new texture analysis tool in Breast MRI

Pooja Joshi
Investigating the role of adenylyl cyclise-associated protein 1 in platelets

Kochar Walladbegi
Nitric oxide regulates myosin light chain phosphatise in blood platelets

Jennifer Rossington
Is efficacy of platelet aggregation inhibition by endogenous endothelial nitric oxide enhanced by ticagrelor mediated P2Y12 blockade?

Shirley Sze
Exercise therapy in heart failure with reduced ejection fraction is safe but did not improve mortality, cardiac mortality or hospitalisation: a meta-analysis

Clement Leung
Novel technique in minimally invasive treatment of varicose veins: Endovenous MechanoChemical Ablation

Laura Broughton
Photoactive Duramycin Conjugate for Targeted Photodynamic Therapy

Andrew McIntosh
Morphological adaptations in the craniomandibular complex of chisel-tooth digging mole-rats